REMARKS

I. Status of the Claims

Claims 1-118, 120-123, 125, 156, 129-151, 154-169, 171-177, 183-185, 187, 189-191, 197, 198 and 200-202 were pending with the July 1, 2010 Office Action. Of those, claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202 are withdrawn and claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-169, 184 and 191 were examined in the July 1, 2010 Office Action. With this Reply, claims 1, 11, 43-45, 54, 59, 60, 97, 120, 125 and 184 are amended. The amendments are made without prejudice or disclaimer and provide no new matter. Support for the amendments is found in the specification at least in FIG. 1, showing a β-glycosylceramide, and the claims as filed. Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-169, 184 and 191are presented for reconsideration.

II. Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 184 is rejected under 35 U.S.C. 112, second paragraph, as lacking antecedent basis for the phrase "said immune-mediated or immune-related disease or disorder". This rejection is moot since the phrase alleged to lack antecedent basis in claim 184 is not present in that claim as amended.

III. Rejection under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-168, 184 and 191 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that the specification does not provide sufficient support for the mammalian intermediary metabolites lipid or glycolipid due to the breadth and diversity of those compounds.

Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

As amended, the claims are directed to treatment with a β-glycosylceramide, which is known as a structurally similar class of compounds that includes the glucocerebroside utilized in the Examples. As such, the claims as amended are not directed to the "enormous diversity of structures" asserted in the Office Action (p. 4) but rather a limited group of structurally similar compounds known to have generally similar biological activities. The extensive studies described in the Examples with glucocerebroside thus provide adequate support for the claims as amended. Withdrawal of the written description rejection under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

IV. Rejection under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-168, 184 and 191 are rejected under 35 U.S.C. 112, first paragraph, enablement requirement. The Office Action asserts that the specification "provides no guidance regarding how the administration of any and all mammalian intermediary metabolites may successfully treat any and all diseases derived from an inflammatory immune response. Applicants request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

Regarding the objection to the breadth of the mammalian intermediary metabolites, Applicants note that the claims as amended are directed only to treatments with β-glycosylceramide, which is known as a structurally similar class of compounds that includes the glucocerebroside utilized in the Examples. As such, the claims as amended involve treatment with a limited group of structurally similar compounds known to have generally similar biological activities. The skilled artisan would therefore understand that the claimed methods would be effective with most if not all mammalian β-glycosylceramides, and any particular β-glycosylceramide could be tested for effectiveness for the instant methods (i.e., as modulating an inflammatory immune

response) without undue experimentation, for example using the methods described in the examples.

Regarding the objection to the breadth of the diseases in the claims, Applicants assert that the Examples clearly show that treatment with β-glycosylceramides reduces inflammation of inflammatory immune responses, at least by inhibiting NKT cells. The skilled artisan would understand that a treatment that reduces inflammation of an inflammatory immune response, as demonstrated in the specification, would likely be an effective treatment for any disease where the pathogenesis of the disease is derived from an inflammatory immune response. This understanding was confirmed by the studies described in the specification for colitis, non-alcoholic steatohepatitis, and diabetes. Those studies confirmed what the skilled artisan would have expected, that the claimed treatment was effective for the three diseases tested, supporting the understanding that the claimed treatment would be effective for any disease where the pathogenesis of the disease is derived from an inflammatory immune response. Additionally, the effectiveness of the treatment for any particular disease could be tested by routine methods.

Relevant to the above arguments that the claims are enabled with respect to the use of any β-glycosylceramide for any disease where the pathogenesis of the disease is derived from an inflammatory immune response, Applicants note that

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

MPEP 2164.08(b). In the present case, while the skilled artisan would expect that any β-glycosylceramide would likely be an effective treatment for any disease where the pathogenesis of the disease is derived from an inflammatory immune response, if some β-glycosylceramides are not effective or some diseases within the scope of the claims are not effectively treated, the claims would nonetheless be enabled, since any specific

β-glycosylceramide or disease could be tested for the effectiveness of the claimed method without undue experimentation. As such, Applicants assert that the claims are enabled for their full scope.

In light of the claim amendments and the above discussion, Applicants respectfully request withdrawal of the enablement rejection under 35 U.S.C. 112, first paragraph.

V. Rejections under 35 U.S.C. § 102

(a) Claims 1, 6, 11, 43-45, 47-52, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157 and 161-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Gizurarson et al. (US 5,942,237) as evidenced by Ogawa et al. (US 5,101,026). The Office Action asserts that Gizurarson et al. "describes a method of inducing an immunomodulatory response in a mammalian subject an effective amount of a mammalian intermediary metabolite ganglioside which comprises a glycolipid, wherein the disease is rhinovirus, influenza, tuberculosis and respiratory syncytial virus...." (Office Action at page 9). Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The claims as amended are directed to methods involving administering a β-glycosylceramide. However, Gizurarson et al. do not teach or suggest the administration of a β-glycosylceramide, since the ganglioside described in that reference for administration (for example at col. 2, lines 45-58) is not a β-glycosylceramide. As such, Gizurarson et al. do not teach or suggest each element of the instant claims as amended, and therefore do not anticipate those claims. Withdrawal of this rejection under 35 U.S.C. 102(b) is therefore respectfully requested.

(b) Claims 1, 6, 11, 43-45, 47-52, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157 and 161-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Belchetz et al. (The Lancet, 1977). The Office Action asserts that "Belchetz et al. describes the

intravenous administration of glucocerebroside in a patient with Gaucher's disease and observed the differential immune responses, including changes in plasma levels of enzymes and liver size....Note that this disease meets a 'metabolic syndrome' and 'any other immune-related or immune mediated disorder' ...." Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The claims as amended are directed to methods involving administering a β-glycosylceramide. However, Belchetz et al. teaches treatment of Gaucher's disease by administration of the enzyme glucocerebroside:β-glucosidase, which is not a β-glycosylceramide. Belchetz et al. does not teach or suggest treating any disease with a β-glycosylceramide. Indeed, since Gaucher's disease is due to a deficiency of that enzyme and the accumulation of glucocerebroside, the skilled artisan would understand that Belchetz et al. teaches away from treating Gaucher's disease with a β-glycosylceramide such as glucocerebroside. As such, Belchetz et al. do not teach or suggest each element of the instant claims as amended, and therefore do not anticipate those claims. Withdrawal of the rejection under 35 U.S.C. 102(b) is therefore respectfully requested.

VI. Rejections under 35 U.S.C. § 103

(a) Claims 1, 6, 11, 43-45, 47-52, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-169 and 184 are rejected under 32 U.S.C. 103(a) as being unpatentable over the combination of Marinier et al. (US 5,747,463) and Gizurarson et al. (discussed under **V.(a)** above) and/or Belchetz et al. (discussed under **V.(b)** above) and as further evidenced by Ogawa et al. (US 5,101,026). The Office Action asserts that, beside the assertions made as discussed under **V.** above with respect to Gizurarson et al. and Belchetz et al., "Marinier discloses the administration of an effective amount of a modified intermediary metabolite comprising a glycolipid to a subject with colitis, wherein the pathogenesis of the disease is derived from an inflammatory immune response...." (Office Action at p. 13). Applicants respectfully request reconsideration

and withdrawal of this rejection in light of the claim amendments and the following discussion.

The Office Action, at page 14, acknowledges that Marinier et al. do not disclose using a mammalian intermediate metabolite. Indeed, Marinier et al. only teach or suggest treatment of any disease with modified glycolipids that are "malonate derivatives" that comprise a $-(CH_2)_p$-$CH(CO_2R^7)_2$ on the sugar constituent (Marinier et al., Abstract). The skilled artisan would thus understand that the unnatural moiety on the sugar constituent is necessary for the described compounds to be "inhibitors of selected-mediated cellular adhesion" (Marinier et al., Abstract) characteristic of the unnatural compounds disclosed therein. Since the compounds described in Marinier et al. would be understood to have the therapeutic activity described therein due to an unnatural moiety present on the compounds, the skilled artisan would understand that it would not have been obvious to "incorporate a known mammalian intermediary metabolite, including a ganglioside or glucocerebroside, in the method taught by Marinier" (Office Action at p. 14) because the skilled artisan would understand that known mammalian intermediary metabolites would likely not have the activity described by Marinier et al. since no mammalian intermediary metabolite has the unnatural moiety present in the compounds described by Marinier et al. that is assumed to be required for the therapeutic activity described therein. Further, as discussed under **V.** above, neither Gizurarson et al. nor Belchetz et al. teach or suggest administering a mammalian intermediate metabolite that is a β-glycosylceramide. Thus, none of the cited references, alone or in combination, teach or suggest administering a mammalian intermediate metabolite that is a β-glycosylceramide. As such, the combination of references do not teach or suggest each element of the instant claims and therefore do not make the instant claims obvious. Withdrawal of this rejection under 35 U.S.C. 103(a) is thus respectfully requested.

(b) Claims 75, 109 and 126 are rejected under 32 U.S.C. 103(a) as being unpatentable over the combination of Marinier et al. (discussed under **(a)** above) and

Gizurarson et al. (discussed under **V.(a)** above) and/or Belchetz et al. (discussed under **V.(b)** above) and as applied to claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 120, 125, 151, 157, 161-169 and 184 and further in view of Das (US 5,869,048) and as further evidenced by Ogawa et al. (US 5,101,026). The Office Action asserts that Marinier et al., Gizurarson et al. and Belchetz et al. teach as described under **(a)** and **V.** above, and that "Das describes a method of vaccinating a human against ulcerative colitis which comprises administering a therapeutically effective amount of a colonic antigen associated with ulcerative colitis obtained from a human." Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The claims are directed to a method comprising administering a mammalian intermediate metabolite that is a β-glycosylceramide for treatment of a disease "wherein the pathogenesis of the disease is derived from an inflammatory immune response." However, as discussed under **(a)** above, neither Marinier et al. nor Gizurarson et al. nor Belchetz et al. teach or suggest any administration of a mammalian intermediate metabolite that is a β-glycosylceramide. As the Office Action acknowledges, Das also does not teach or suggest any administration of a mammalian intermediate metabolite that is a β-glycosylceramide. Thus, none of the cited references, alone or in combination, teach or suggest administering a mammalian intermediate metabolite that is a β-glycosylceramide. As such, the combination of references do not teach or suggest each element of the instant claims and therefore do not make the instant claims obvious. Withdrawal of this rejection under 35 U.S.C. 103(a) is thus respectfully requested.

(c) Claims 54, 76 and 191 are rejected under 32 U.S.C. 103(a) as being unpatentable over the combination of Marinier et al. (discussed under **(a)** above) and Gizurarson et al. (discussed under **V.(a)** above) and/or Belchetz et al. (discussed under **V.(b)** above) and as applied to claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 120, 125, 151, 157, 161-169 and 184 and further in view of Collins et al. (US Publ. 20020141977) and

Liotta et al. (US 6,610,835) as further evidenced by Ogawa et al. (US 5,101,026). The Office Action asserts that Marinier et al., Gizurarson et al. and Belchetz et al. teach as described under **(a)** and **V.** above, and that "Collins describes a general method of immunotherapy based on antigen presenting cells including dendritic cells for the prevention and/or treatment of various diseases such as inflammatory diseases" and "Liotta discloses that sphinogolipids are found in a number of foods, including wheat flour, potato and beans...." (both quotes from Office Action at page 19). Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The claims are directed to a method comprising administering a mammalian intermediate metabolite that is a β-glycosylceramide for treatment of a disease "wherein the pathogenesis of the disease is derived from an inflammatory immune response." However, as discussed under **(a)** above, neither Marinier et al. nor Gizurarson et al. nor Belchetz et al. teach or suggest any administration of a mammalian intermediate metabolite that is a β-glycosylceramide. As the Office Action acknowledges. Collins et al. and Liotta et al. also do not teach or suggest any administration of a mammalian intermediate metabolite that is a β-glycosylceramide. Thus, none of the cited references, alone or in combination, teach or suggest administering a mammalian intermediate metabolite that is a β-glycosylceramide. As such, the combination of references do not teach or suggest each element of the instant claims and therefore do not make the instant claims obvious. Withdrawal of this rejection under 35 U.S.C. 103(a) is thus respectfully requested.

VII. Double Patenting Rejections

Claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 109, 120, 125, 151, 157 and 161-169 are provisionally rejected on the ground of obviousness-type double patenting (ODP) as being unpatentable over claims 1, and 4-6 of copending Application No. 10/375,906 in view of Stephenson and Zambon (Occup. Med, 2002). Also, claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 109, 120, 125, 151, 157 and 161-169 are provisionally rejected on the

ground of obviousness-type double patenting (ODP) as being unpatentable over claims 12, 15-17 and 22-24 of copending Application No. 10/733,488 in view of Stephenson and Zambon (Occup. Med, 2002) and Hansen-Flaschen (Ann Intern Med, 2003). Additionally, claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 109, 120, 125, 151, 157 and 161-169 are provisionally rejected on the ground of obviousness-type double patenting (ODP) as being unpatentable over claims 50-52, 55, 57, 59 and 62 of copending Application No. 10/733,489 in view of Stephenson and Zambon (Occup. Med, 2002) and Hansen-Flaschen (Ann Intern Med, 2003). Further, claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 109, 120, 125, 151, 157 and 161-169 are provisionally rejected on the ground of obviousness-type double patenting (ODP) as being unpatentable over claims 1-4, 9-11, 21-25, 27-31, 36-38, 48 and 49 of copending Application No. 11/287,502. Still further, claims 1, 6, 11, 43-45, 47-52, 59, 60, 97, 109, 120, 125, 151, 157 and 161-169 are provisionally rejected on the ground of obviousness-type double patenting (ODP) as being unpatentable over claims 1, 2 and 5 of copending Application No. 12/746,430. Since these rejections are dependent on the scope of both the instant claims and the claims in the cited applications, Applicants will provide a terminal disclaimer where necessary when a proper ODP rejection is the only rejection remaining in this application.

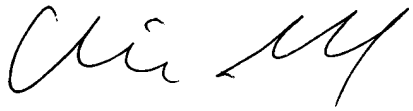
VIII. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections of record and passage of all claims to allowance.

Applicants authorize the United States Patent and Trademark Office to charge all fees required to maintain pendency of this application, including the extension of time fees, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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